

by changes in the technique of reversal. In many of parts of Britain over 85% of sterilisations are now carried out laparoscopically, and many of these operations entail the application of clips to the fallopian tubes rather than the more destructive methods of unipolar or bipolar diathermy, thermal coagulation, or the application of rings.<sup>12</sup> The search for a truly reversible method of sterilisation has continued unsuccessfully ever since Aldridge described his "extra-peritoneal fimbriopexy" over 50 years ago.<sup>13</sup>

To the patient contemplating reversal today one clip at the mid-isthmic portion of each fallopian tube offers the best hope because the success of reversal is related, firstly, to the length of tube remaining and, secondly, to the site of the anastomosis. "Cut and tie" surgical methods and unipolar diathermy often destroy at least 4 cm of the fallopian tube and rings occlude about 2 cm but clips damage no more than 5 mm.<sup>14</sup> Successful repair needs a tube, with intact fimbriae, of at least 4 cm<sup>5</sup> and preferably 6 cm<sup>15</sup> after reanastomosis. An isthmoisthmic anastomosis is the most likely to be successful as there is little or no luminal disparity and ciliary action is probably not as important as in the ampulla.<sup>5</sup> Although mucosal flattening, absence of cilia, and polyposis have been found in the tubes of patients sterilised over five years previously,<sup>16</sup> the interval between sterilisation and reversal does not apparently affect the chances of success.<sup>6</sup><sup>15</sup>

Microsurgical techniques have been applied to the fallopian tubes since the early 1970s, and the principles of adequate exposure, scrupulous haemostasis, constant irrigation, minimal trauma, and careful placement of fine sutures are well established.<sup>17</sup> Individual microsurgeons do, however, differ in the details of techniques of anastomosis—particularly whether to use splints, which suture material to use, where to site sutures, and whether to use adjuvant treatment to avoid adhesion formation. Most surgeons find that magnification helps them create even the easiest anastomoses,<sup>17</sup> but no difference has been shown between results obtained with operating microscopes and those obtained with loupes.<sup>18</sup> Surgical technique is more important than the type of optical aid used, and the best training is a combination of laboratory and operating theatre experience.<sup>17</sup> "Practice makes perfect," yet most gynaecologists receive few requests for reversal surgery: services should perhaps be centralised.<sup>6</sup><sup>19</sup>

Careful counselling of any patient requesting sterilisation is essential, particularly in women under 30. The permanent nature of the operation must be emphasised. The gynaecologist who performs a sterilisation must use an effective technique but one which causes minimal trauma—so that reversal is more likely to be successful should the patient's circumstances change.

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- 1 Chamberlain G, Carron Brown J, eds. *Gynaecological laparoscopy*. London: Royal College of Obstetricians and gynaecologists, 1978.
- 2 Henderson SR. The reversal of female sterilization with the use of microsurgery: a report on 102 patients with more than one year of follow up. *Am J Obstet Gynecol* 1984;149:57-65.
- 3 Antoine JM, Dubuisson JB, Tournaire M, Lerat H. Request for reversal of tubal sterilization. Survey conducted by the National College of French Gynecologists and Obstetricians. *J Gynecol Obstet Biol Reprod (Paris)* 1983;12:583-91.
- 4 Siegler AN, Perez RJ. Reconstruction of fallopian tubes in previously sterilized patients. *Fertil Steril* 1975;26:383-92.
- 5 Paterson PJ. Factors influencing the success of microsurgical tuboplasty for sterilization reversal. *Clin Reprod Fertil* 1985;3:57-64.
- 6 Boeckx W, Gordts S, Buyss K, Brosens I. Reversibility after female sterilization. *Br J Obstet Gynaecol* 1986;93:839-42.
- 7 Winston RML. Reversal of tubal sterilization. *Clin Obstet Gynecol* 1980;23:1261-8.
- 8 Quinlan DK. A profile of 125 women requesting reversal of sterilization. *S Afr Med J* 1985;68:243-4.
- 9 Divers WA. Characteristics of women requesting reversal of sterilization. *Fertil Steril* 1984;41:233-6.

- 10 Bledin KD, Cooper JE, Mackenzie S, Brice B. Psychological sequelae of female sterilization: short-term outcome in a prospective controlled study. A report from the UK Field Research Centre of a WHO collaborative project. *Psychol Med* 1984;4:379-90.
- 11 Winston RML. Why 103 women asked for reversal of sterilisation. *Br Med J* 1977;iii:305-7.
- 12 Anonymous. Female sterilisation—no more tubal coagulation. [Editorial.] *Br Med J* 1980;i:1037.
- 13 Aldridge AH. Temporary surgical sterilization with subsequent pregnancy. *Am J Obstet Gynecol* 1934;27:741-5.
- 14 Newton JR. Sterilization. *Clin Obstet Gynaecol* 1984;11:603-40.
- 15 Spivak MM, Librach CL, Rosenthal DM. Microsurgical reversal of sterilization: a six year study. *Am J Obstet Gynecol* 1986;154:355-61.
- 16 Vasquez G, Winston RML, Boeckx W, Brosens I. Tubal lesions subsequent to sterilization and their relation to fertility after attempts at reversal. *Am J Obstet Gynecol* 1980;138:86-92.
- 17 Winston RML. Progress in tubal surgery. *Clin Obstet Gynaecol* 1981;8:653-80.
- 18 Rock JA, Bergquist CA, Kimball AWJ, Zacur HA, King TM. Comparison of the operating microscope and loupe for microsurgical tubal anastomosis: a randomized clinical trial. *Fertil Steril* 1984;41:229-32.
- 19 Boeckx W, Gruft L, Brosens I. Training in tubal microsurgery. *Br J Obstet Gynaecol* 1985;92:266-9.

## Cannabis: dangers and possible uses

Cannabis is a prime example of a pharmacologically "dirty" drug. It contains many active substances with multiple effects and several (unknown) mechanisms of action. Cannabinoids exert psychotropic, hypnotic, tranquillising, anti-emetic, anticonvulsant, and analgesic effects; they lower intraocular pressure, increase appetite, and affect the cardiovascular, respiratory, reproductive, and immune systems. Is it possible to separate adverse from desirable effects and so to harness this chameleon for therapeutic benefit?

The psychotropic effects of cannabis are largely reproducible by  $\Delta^9$ -tetrahydrocannabinol, the most potent psychoactive ingredient.<sup>1</sup> Its hedonic properties are well known and have long been exploited for recreational purposes, but dysphoric reactions are common. Acute exposure even to moderate doses of cannabis and  $\Delta^9$ -tetrahydrocannabinol, especially in those not used to taking the drug, can precipitate anxiety and panic reactions, depersonalisation, and schizophreniform, manic, and confusional psychoses.<sup>2,5</sup> Certain personality characteristics and environmental stress predispose to such reactions, but they can occur in patients without a psychiatric history.<sup>5-7</sup> Cannabis can precipitate schizophrenic illness and aggravate schizophrenia in patients controlled on neuroleptics<sup>8</sup>—possibly it antagonises some antipsychotic drug effects.<sup>8,9</sup> "Flashback" and recurrence of dysphoria during drug abstinence may occur after heavy cannabis exposure.<sup>3</sup>

Whether chronic cannabis use causes brain damage remains controversial. Persistent neuronal ultrastructural abnormalities and electroencephalographic changes have been observed in rats and primates after chronic cannabis exposure,<sup>2,10</sup> but a report of cerebral atrophy in human cannabis smokers<sup>11</sup> was not confirmed by studies using computed tomography,<sup>12-14</sup> electroencephalography,<sup>15</sup> and blood flow techniques.<sup>3</sup> Nevertheless, most reports agree that heavy chronic cannabis users can develop an amotivational syndrome, with apathy and loss of academic performance in students.<sup>1-3</sup> Since cannabis is concentrated in the limbic system,<sup>17</sup> the motivational centre in the brain, and interferes with memory, cognition, and psychomotor performance<sup>12</sup> such an effect is not surprising. The syndrome is probably reversible on stopping smoking cannabis.<sup>13</sup> Withdrawal of cannabis after chronic use gives rise to an abstinence syndrome similar to that seen after withdrawal of benzodiazepines and hypnotics.<sup>3,18</sup>

Cannabis presents other hazards for casual and chronic users. Even social doses seriously impair car driving and aeroplane flying ability because of distortions of time and space estimation, reduced vigilance, and incoordination<sup>1,2</sup>—and effects persist for many hours because the drug is eliminated slowly.<sup>19</sup> Cardiovascular effects include appreciable tachycardia,<sup>20</sup> hypotension,<sup>2</sup> and hypertension<sup>21</sup>; these changes may precipitate angina or even death<sup>20</sup> in predisposed individuals. Cannabis smoke is irritating to bronchial mucosa and may be more carcinogenic than tobacco smoke.<sup>1</sup> The drug depresses reproductive function in both sexes,<sup>2</sup> and  $\Delta^9$ -tetrahydrocannabinol crosses the placenta and enters breast milk.<sup>2</sup> There is, however, no definite evidence of teratogenicity in man.<sup>22</sup> Cannabis also has immunodepressant effects, inhibiting T cell function.<sup>2</sup>

Those most at risk of the psychiatric effects of cannabis seem to be young teenagers, heavy daily users, psychiatric patients,<sup>3</sup> and those with emotional disturbances or who are undergoing environmental stress.<sup>6</sup> Physical risks apply particularly to car drivers and those with cardiovascular disease. Doctors should consider these factors when advising cannabis smokers or their parents.

Despite initial hopes<sup>23</sup> the therapeutic use of cannabinoids remains limited.  $\Delta^9$ -Tetrahydrocannabinol,<sup>24</sup> nabilone,<sup>25</sup> the tetrahydrocannabinol analogue (BRL-4664),<sup>26</sup> and levonantradol<sup>27-29</sup> have been used as antiemetics for patients taking cytotoxic drugs. They are as effective as phenothiazines, with which they may be combined, but the incidence of adverse effects is high—a third of patients in some studies experiencing dysphoria and 90% somnolence.<sup>27</sup> Immunosuppression is a theoretical risk. Levonantradol is an effective analgesic for postoperative pain<sup>30</sup> and pain caused by cancer<sup>31</sup> but at the cost of adverse effects. Cannabinoids attenuate morphine withdrawal signs in animals by a non-opioid mechanism,<sup>32,33</sup> but this effect has not been explored in man. Oral cannabinoids are probably unsuitable for lowering intraocular tension in glaucoma,<sup>34</sup> and topical solutions require further development.<sup>35,36</sup> Cannabidiol is effective in some cases of generalised epilepsy refractory to other anticonvulsants<sup>37</sup> and potentiates the effect of diazepam and valproic acid in animals.<sup>9,38</sup> but further human studies are needed. Cannabinoids may eventually be used for anxiety,<sup>39</sup> insomnia,<sup>37</sup> muscle spasticity,<sup>40</sup> and bacterial and fungal infections<sup>41</sup> but probably not as antihypertensive agents,<sup>21</sup> bronchodilators,<sup>2</sup> or appetite stimulants for those with anorexia nervosa.<sup>42</sup>

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1 Murray JB. Marijuana's effects on human cognitive functions, psychomotor functions, and personality. *J Gen Psychol* 1986;113:23-5.

2 Maykut MD. Health consequences of acute and chronic marihuana use. *Prog Neuro-psychopharmacol Biol Psychiatry* 1985;9:209-38.

3 Tunving K. Psychiatric effects of cannabis use. *Acta Psychiatr Scand* 1985;72:209-17.

- 4 Carney MWP, Baccelle L, Robinson B. Psychosis after cannabis abuse. *Br Med J* 1984;288:1047.
- 5 Szymanski HV. Prolonged depersonalisation after marijuana use. *Am J Psychiatry* 1981;138:231-3.
- 6 Gerston SP. Long-term adverse effects of brief marijuana usage. *J Clin Psychiatry* 1980;41:60-1.
- 7 Koukkou M, Lehmann D. Correlations between cannabis-induced psychopathology and EEG before and after drug ingestion. *Pharmacopsychiatry* 1978;11:220-7.
- 8 Knudsen P, Vilman T. Cannabis and neuroleptic agents in schizophrenia. *Acta Psychiatr Scand* 1984;69:162-74.
- 9 Leader JP, Koe BK, Weissman A. GABA-like actions of levonantradol. *J Clin Pharmacol* 1981;21(suppl 8-9):262-70S.
- 10 McGeer PC, Jakubovic A. Ultrastructural and biochemical changes induced by marihuana. In: Nahas GG, Paton WDM, eds. *Marihuana: biological effects*. Oxford: Pergamon Press, 1979:519-31.
- 11 Campbell AMG, Evans M, Thomson JLG, Williams MJ. Cerebral atrophy in young cannabis smokers. *Lancet* 1971;ii:1219-24.
- 12 Kuehnle J, Mendelson JH, Davis KR, New PFJ. Computed tomographic examination of heavy marijuana smokers. *JAMA* 1977;237:1231-2.
- 13 Co BT, Goodwin DW, Gado M, Mikhael M, Hill SY. Absence of cerebral atrophy in chronic cannabis users. Evaluation by computerised transaxial tomography. *JAMA* 1977;237:1229-30.
- 14 Hannerz J, Hindmarsh T. Neurological and neuroradiological examination of chronic cannabis smokers. *Ann Neurol* 1983;13:207-10.
- 15 Fink M. Effects of acute and chronic inhalation of hashish, marijuana, and  $\Delta^9$ -tetrahydrocannabinol on brain electrical activity in man: evidence for tissue tolerance. *Am NY Acad Sci* 1976;282:387-98.
- 16 Karacan I, Fernandez-Salas, Coggins WJ, et al. Sleep electroencephalographic-electrocardiographic characteristics of chronic marijuana users: Part I. *Ann NY Acad Sci* 1976;282:348-74.
- 17 McIsaac WM, Fritchie GE, Idanpaan-Heikkila, Ho BT, Englert LF. Distribution of marijuana in the monkey brain and concomitant behavioural effects. *Nature* 1971;230:593-5.
- 18 Jones RT, Benowitz NL, Herning RI. Clinical relevance of cannabis tolerance and dependence. *J Clin Pharmacol* 1981;21(suppl 8-9):143-52S.
- 19 Wall ME, Perz-Reyes M. The metabolism of  $\Delta^9$ -tetrahydrocannabinol and related cannabinoids in man. *J Clin Pharmacol* 1981;21(suppl 8-9):178-9S.
- 20 Macinnes DC, Miller KM. Fatal coronary artery thrombosis associated with cannabis smoking. *J R Coll Gen Pract* 1984;34:575-6.
- 21 Benowitz NL, Jones RT. Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. *J Clin Pharmacol* 1981;21(suppl 8-9):214-23S.
- 22 Schardein JL. *Chemically induced birth defects*. New York: Marcel Dekker, 1985:779.
- 23 Bateman DN, Rawlins MD. Therapeutic potential of cannabinoids. *Br Med J* 1982;284:1211-1.
- 24 Orr LE, McKernan JF. Antiemetic effect of  $\Delta^9$ -tetrahydrocannabinol in chemotherapy-associated nausea and emesis as compared to placebo and compazine. *J Clin Pharmacol* 1981;21(suppl 8-9):76-80S.
- 25 Einhorn LH, Nagy C, Furnas B, Williams SD. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. *J Clin Pharmacol* 1981;21(suppl 8-9):64-9S.
- 26 Staquet M, Bron D, Rozenzweig M, Kemis Y. Clinical studies with a THC analog (BRL-4664) in the prevention of cisplatin-induced vomiting. *J Clin Pharmacol* 1981;21(suppl 8-9):60-3S.
- 27 Diasio RB, Ettinger DS, Satterthwaite RN. Oral levonantradol in the treatment of chemotherapy-induced emesis: preliminary observations. *J Clin Pharmacol* 1981;21(suppl 8-9):81-5S.
- 28 Cronin CM, Sallan SE, Gelber R, Lucas VS, Laszlo J. Antiemetic effect of intramuscular levonantradol in patients receiving anticancer chemotherapy. *J Clin Pharmacol* 1981;21(suppl 8-9):43-50S.
- 29 Laszlo J, Lucas VS, Hanson DC, Cronin C, Sallan SE. Levonantradol for chemotherapy-induced emesis: phase I-II oral administration. *J Clin Pharmacol* 1981;21(suppl 8-9):51-6S.
- 30 Jain AK, Ryan JR, McMahon FG, Smith G. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol* 1981;21(suppl 8-9):320-6S.
- 31 Noys R Jr, Brunk SF, Avery DAH, Canter A. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther* 1975;18:84-9.
- 32 Lal H, Bennett DA, Shearman GT, McCarten MD, Murphy R, Angeja A. Effectiveness of nantadol in blocking narcotic withdrawal signs through non-narcotic mechanisms. *J Clin Pharmacol* 1981;21(suppl 8-9):361-6S.
- 33 Chesser GB, Jackson DM. The quasi-morphine withdrawal syndrome: effect of cannabidiol, cannabidiol and tetrahydrocannabinol. *Pharmacol Biochem Behav* 1985;23:13-5.
- 34 Merrit JC, Perry DD, Russell DN, Jones BF. Topical  $\Delta^9$ -tetrahydrocannabinol and aqueous dynamics in glaucoma. *J Clin Pharmacol* 1981;21(suppl 8-9):467-71S.
- 35 Cohen S. An overview of the symposium. *J Clin Pharmacol* 1981;21(suppl 8-9):486-7S.
- 36 Razdan RK, Howes JF, Pars HG. Development of orally active cannabinoids for the treatment of glaucoma. *Natl Inst Drug Abuse Res Monogr Ser* 1983;43:157-63.
- 37 Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol* 1981;21(suppl 8-9):417-27S.
- 38 Ehlers CL, Henriksen SJ, Bloom FE. Levonantradol potentiates the anticonvulsant effects of diazepam and valproic acid in the Kindling model of epilepsy. *J Clin Pharmacol* 1981;21(suppl 8-9):406-12S.
- 39 Fabre LF, McLendon D. The efficacy and safety of nabilone (a synthetic cannabinoid) in the treatment of anxiety. *J Clin Pharmacol* 1981;21(suppl 8-9):377-82S.
- 40 Petro DJ, Ellenberger C. Treatment of human spasticity with  $\Delta^9$ -tetrahydrocannabinol. *J Clin Pharmacol* 1981;21(suppl 8-9):413-16S.
- 41 Turner CE, Elsohly MA. Biological activity of cannabichromene, its homologs and isomers. *J Clin Pharmacol* 1981;21(suppl 8-9):283-91S.
- 42 Gross H, Ebert MH, Faden VB, et al. A double-blind trial of  $\Delta^9$ -tetrahydrocannabinol in primary anorexia nervosa. *J Clin Psychopharmacol* 1983;3:165-71.